

In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill in the art is charged with knowledge of the entire body of technological invention, including that which might lead away from the claimed invention." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988) (emphasis added).

Applicants have already cited a number of documents in which skilled artisans have explicitly averred the unexpectedness of the observed high therapeutic index in the "non-natural" (-)-enantiomer of this invention (see applicants' July 23, 1993 response to the February 23, 1993 Office Action, pages 8-9). Applicants have also cited various documents -- including the '466 patent which would suggest to one of skill in the art that the non-natural enantiomer is inactive\* -- which teach away from the claimed invention by suggesting that nonnatural enantiomers of nucleoside analogues are either inactive or have substantially reduced activity (see Table 1 in applicants' July 23, 1993 response and applicants' March 15, 1994 response to the September 15, 1993 Office Action, page 5, line 28 to page 6, line 11). In fact, the '466 patent itself explicitly teaches away from this invention by regarding one of the enantiomers as a "50% impurity":

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\* The Examiner contends that "[t]he figures, schemes and formulas [illustrating the (+)-enantiomer throughout the '466 patent] are not required to reflect the configuration". However, to those of skill in the art, they do. Chemical figures and formulas are the most common means by which scientists communicate about chemical compounds. This is especially true when issues of stereochemistry -- relating to three-dimensional disposition of objects -- are discussed. The standard by which any piece of prior art is to be measured is that of one with ordinary skill in the art. One of ordinary skill in the art would read the '466 patent with an eye to the structural formulas disclosed in the patent. Those formulas consistently illustrate the "natural" nucleoside configuration -- that of the (+)-enantiomer, not the (-)-enantiomer of this invention. Thus, the disclosure of the '466 patent provides ample evidence that the (-)-enantiomer was considered a "50% impurity".

"[T]here exists a need for a stereoselective synthetic route to enantiomerically-enriched  $\beta$ -BCH-189 because the other enantiomer is inactive and, therefore, represents a 50% impurity". The '466 patent, column 3, lines 53-56.

Clearly, the patentees did not appreciate that the two enantiomers have comparable activity, regardless to which enantiomer configuration the term "impurity" may refer. Applicants have also submitted a declaration by Dr. Richard Storer ("Storer Declaration" dated March 11, 1994, submitted with applicants' March 15, 1994 response) which outlines the level of skill in the art at the time this invention was made (Storer Declaration, paragraphs 4-6) and explains why the observed antiviral activity of the (-)-enantiomer of this invention was surprising and unexpected. The Examiner has not acknowledged the Storer Declaration and the Final Office Action is silent on the cited documents explicitly supporting the nonobviousness of the present invention.

Second, the rejection should be withdrawn because it ignores the evidence demonstrating the low toxicity profile of the claimed (-)-enantiomer. Even if one assumes *arguendo* that it was obvious to test all stereoisomers of an active stereorandom mixture, it was still unexpected to find an active nucleoside analogue with a therapeutic index as high as that observed for the (-)-enantiomer of this invention. The Storer Declaration (paragraph 8) also explains that the low toxicity of the (-)-enantiomer (corresponding to a high therapeutic index) was "entirely unexpected". On this issue, the Final Office Action is again nonresponsive to the Storer Declaration or any of the other evidence cited in the July 23, 1993 response (pages 8-9).

Applicants request that the Examiner reconsider and withdraw the final rejection in view of the Storer Declaration and the unequivocal statements of independent experts in the field of nucleoside chemistry and pharmacology cited in previous responses to Office Actions.

The Examiner has also maintained the rejection under 35 U.S.C. §§ 102 and 103 over United States patent 5,047,407 ("the '407 patent") without providing any reasons as to why applicants' March 25, 1994 response and arguments against that rejection were not deemed convincing. Applicants note that the '407 patent, like the '466 patent, discloses a racemic form of the compound claimed in this application. The claims of this application are patentable over the racemic mixture of the '407 patent for the same reasons that they are patentable over the racemic mixture of the '466 patent, as explained above. Accordingly, applicants request that the Examiner withdraw the rejection.

For the foregoing reasons, applicants believe that the amended claims are in condition for allowance and request that the Examiner withdraw all rejections and allow this application.

Respectfully submitted,

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